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Sodium Oxybate in Narcolepsy with Cataplexy: Zurich Sleep Center Experience

R. Poryazova[a] S. Tartarotti[a] R. Khatami[b] C.R. Baumann[a] P. Valko[a]
U. Kallweit[a] E. Werth[a] C.L. Bassetti[a, c]

[a]Department of Neurology, University Hospital Zurich, Zurich, [b]Sleep Clinic, Barmelweid, and
[c]Department of Neurology, Neurocenter (EOC) of Southern Switzerland, Ospedale Civico, Lugano, Switzerland

Key Words
Narcolepsy · Cataplexy · Excessive daytime sleepiness · Sleep paralysis · Hallucinations · Sodium oxybate

Abstract
Sodium oxybate (SO; Xyrem®) has been approved in most countries for treatment of narcolepsy and cataplexy. In this study, we present a single-center experience of a series of 18 patients with narcolepsy with cataplexy (18/18 DQB1*0602 positive, 17/17 with low/absent cerebrospinal fluid hypocretin) in whom SO was prescribed. After 26 ± 13 months, 13/18 patients were still on SO at a mean dosage of 6.1 ± 1.2 g (in 8 of them in combination with stimulants). The following significant effects were observed: improved subjective sleepiness (12/13), cataplexy (13/13; median number of attacks from 20 to 1/month), hallucinations (8/10) and sleep paralysis (8/8); increase in mean sleep latency on the Maintenance of Wakefulness Test (from 5.5 to 17.4 min) and sleep/rest efficiency on actigraphy (from 61 to 76%); decrease in Epworth Sleepiness Scale score (from 18 to 14), sleep onset REM periods on the Multiple Sleep Latency Test (from 3.6 to 2.4) and errors in the Steer-Clear Test (from 11 to 2%). Five patients discontinued SO because of insufficient compliance (n = 2), lack of efficiency (n = 1) and side effects (n = 1). These data confirm and expand previous reports on the good effects and tolerability of SO as a treatment for narcolepsy with cataplexy.

Introduction

Narcolepsy with cataplexy (NC) is a disabling life-long sleep-wake disorder, characterized by excessive daytime sleepiness (EDS) and sudden loss of muscle tone triggered by emotions (cataplexy) [1]. Additional symptoms include sleep paralysis, hypnagogic hallucinations and fragmented nighttime sleep. Cataplexy is specific for narcolepsy and its presence allows diagnosing NC on clinical grounds. Typical paraclinical findings with diagnostic significance include the occurrence of two or more sleep-onset REM periods (SOREMPs) in the multiple sleep latency test (MSLT) [2], association to the HLA-DQB1*0602 (found in 98% of NC compared to 35% of healthy controls) [3] and decrease of CSF hypocretin (levels <110 pg/ml are considered low or undetectable, between 110 and 200 pg/ml intermediate and levels >200 pg/ml are con-

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Claudio L. Bassetti, MD
Department of Neurology
Neurocenter (EOC) of Southern Switzerland, Ospedale Civico
Via Tesserete 46, CH–6903 Lugano (Switzerland)
Tel. +41 91 811 6658, E-Mail claudio.bassetti@eoc.ch

sidered normal) [4]. The conventional treatment is symptomatic and includes stimulant drugs (amphetamine analogs and modafinil) targeting EDS and antidepressants to treat cataplexy [5]. Sodium oxybate (SO), also known as γ-hydroxybutyrate (GHB), is a new approach to treat all symptoms of the disease. It has been suggested that GHB has a role as a neurotransmitter or neuromodulator in the mammalian brain [6] and specific high-affinity binding sites have been identified in hippocampus, ventrolateral thalamus and the frontoparietal and entorhinal cortex of the rat brain [7].

GHB was first synthesized in 1960 and was shown to cross the blood-brain barrier rapidly to induce a sleep-like state with cardiovascular stability. In 1964, the substance was introduced as an intravenous anesthetic but was never largely accepted because of the high incidence of side effects (vomiting, seizures). In 1967, it was hypothesized that GHB might be beneficial for the treatment of sleep disorders [8]. Broughton and Mamelak [9, 10] decided to use GHB to normalize nighttime sleep in narcolepsy patients and thus to improve the daytime symptoms of the disease. These and following studies [11–13] demonstrated that the bedtime administration of GHB improved nighttime sleep but also daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis. Parallel to these studies, reports appeared that GHB enhanced the effect of steroids and the release of growth hormone [14]. As a consequence, the drug was used by bodybuilders and for strength training. After the reports of a few fatal overdose cases in bodybuilders, GHB was banned by the American Food and Drug Administration (FDA) in 1990. This was followed by illicit use of GHB as a recreational drug because of its euphoric effects, disinhibition and sexual arousal. It was also implicated in a number of sexual assault cases and was labeled as 'date rape drug'. Especially in combination with alcohol GHB, causes anterograde amnesia and the victims are unable to recall any details of the event. In Switzerland, mainly cases with acute GHB intoxication have been reported [15–17]. According to the GHB fact-sheet, issued by the Swiss National Health Organization (Bundesamt für Gesundheit, BAG) between 1997 und 2005, 334 cases with GHB intoxication were reported to the Swiss Toxicological Information Centre, of which only 1 was fatal [18]. Recently, 3 fatal cases in patients with NC (n = 2) and sleep apnea (n = 1) treated with SO were reported [19], but the link with SO was not clear in any of them [20].

In 1994, Orphan Medical began the development of SO oral solution and after the safety and the efficacy of the drug for the treatment of narcolepsy were established in two multicenter, double-blind, placebo-controlled, randomized trials [21, 22], the FDA approved it for the treatment of cataplexy in narcolepsy in 2002 and for the treatment of EDS in 2005. In 2005, SO was also approved by the European Medicines Agency (EMEA). Swissmedic approved it in Switzerland in 2006. In the mean time, the long-term efficacy [23] and the effect of SO on daytime alertness have been shown [24–27]. Based on A-level evidence, SO has been recommended as a first-line treatment for cataplexy in NC by the European Federation of Neurological Societies (EFNS) Task Force [28].

In this study, we present our own experience in the treatment of NC patients with SO.

Patients and Methods

Eighteen HLA-DQB1*0602-positive (18/18), hypocretin-deficient (17/17) NC patients (9 men), mean age 43 years ± 16 (SD), mean disease duration 14 ± 14 years, were treated with SO because of persistent/severe cataplexy (n = 18/18) and EDS (n = 18/18). Disturbed nighttime sleep was reported in 17/18 patients. The Epworth sleepiness score (ESS), frequency of cataplexy, sleep paralysis, hallucinations and nightmares were assessed before and after treatment. Video-polysomnography (PSG) was performed in 17/18 patients before treatment and in 6/18 patients after treatment, MSLT in 16/18, respectively in 10/18, maintenance of wakefulness test (MWT) and actigraphy in 15/18, respectively in 10/18, and steer-clear vigilance test (SCVT) in 14/18, respectively in 10/18 patients.

PSG consisted of four-channel EEG (C3/A2, C4/A1, O1/A2, O2/A1), left and right electrooculography (EOG), submental electromyography (EMG), electrocardiography (ECG), respiratory flow and effort, pulse oximetry and left and right anterior tibialis EMG. All recordings were done on Embla Somnologica™ Studio. Sleep stages, apneas/hypopneas, periodic limb movements and arousals were scored manually according to international criteria [2, 29–31]. Sleep onset was defined as the first epoch of either NREM-2 or REM sleep.

Standard MSLT [32] was performed on the day following the nocturnal recording, starting 2 h after waking up. For each patient, four or five naps with a duration of 20 min in 2-hour intervals were recorded. The naps were terminated after 20 min. MWT was performed at daytime, for each patient four naps, each with a maximal duration of 40 min in 2-hour intervals were recorded. In case the patient fell asleep, the recording was interrupted after three consecutive epochs of NREM-1 or after one epoch of any other sleep stage. Sleep onset for both MSLT and MWT was defined as the first epoch of sleep.

Fourteen-day actigraphy was performed using Actiwatch® (Cambridge Neurotechnology); the main parameter of interest was the sleep/rest efficiency in percent. Vigilance during a monotonous task was assessed using the steer-clear vigilance test (SCVT) computer program [33]. For SCVT an arbitrary cut-off of

3% has been accepted in different sleep laboratories as normal controls usually lie clearly below this value [33].

Statistical analysis was performed using SPSS 15 software. χ^2, paired t tests and Wilcoxon signed rank tests were used to analyze categorical and continuous variables, respectively. Significance level was set at $p < 0.05$.

Results

All patients were HLA-DQB1*0602-positive and in 17/18, CSF levels of hypocretin-1 were measured. It was undetectable in 13, low in 3, and intermediate in 1 patient. ESS was assessed in all patients at baseline. All patients reported cataplexy with a monthly frequency ranging form 1 to 600 (median 16, mean 101). Sleep paralysis was reported in 11/18 patients, hypnagogic hallucinations in 14/18, nightmares in 4/18 and disturbed nighttime sleep in 17/18 patients. The demographics, ESS, PSG, MSLT, MWT, actigraphy and SCVT data for all patients prior to treatment are shown in table 1.

Patients on Sodium Oxybate

Thirteen out of 18 patients are still treated with SO (7 men, mean dosage 6.4 ± 1.2 g, mean treatment duration 26 ± 13 months). Additional therapies include modafinil (n = 5), fluoxetine (n = 1) and methylphenidate (n = 1). One patient stopped modafinil after the initiation of SO, in all the others the additional therapies remained stable.

One patient reported overall improvement of the narcolepsy symptoms of about 80% with one single bedtime dose of 5 g SO. Another 2 patients admitted skipping the second dose occasionally but in spite of that did not notice any significant difference in their symptoms. The remaining 10 patients reported taking SO regularly twice – at bedtime and between 2.5 and 4 h later.

Nearly all patients (12/13) reported subjective improvement in EDS (from 20 to 80%, mean 33 ± 23%). ESS significantly improved (from 17.9 to 13.9, $p = 0.001$). After treatment, 6/13 patients were free of cataplexy, in 7/13 patients a marked reduction in cataplexy frequency, duration and severity was observed. Cataplexy under SO usually occurred later in the day, when the patients were tired. In general the improvement of cataplexy was highly significant (median before treatment 20 per month, after treatment 1, $p = 0.001$). The reduction in percent was between 50 and 100%, mean ± SD, 88 ± 19%. Sleep paralyses disappeared in 8/8 patients after initiation of SO. Under SO treatment, 8/10 patients were free of hallucinations, 2 patients reported significant reduction in the frequency of hallucinations. Nightmares disappeared in 3

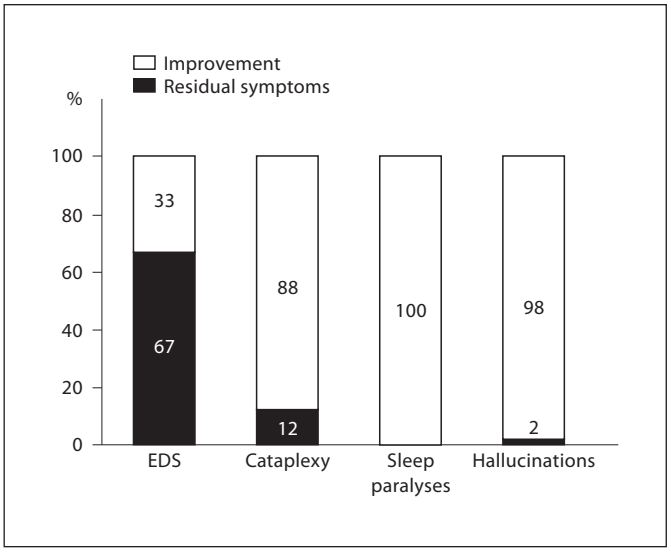

Fig. 1. Improvement of clinical symptoms after treatment, in percent.

Table 1. Characteristics of the patients prior to treatment with SO

Variable	Mean ± SD	Range
Age, years	43 ± 16	18–69
Male gender	9	
Disease duration, years	14 ± 14	2–50
ESS	17 ± 4	9–24
Cataplexy frequency per month, median	16	1–600
Sleep paralysis per month	5 ± 9	0–30
Hallucination frequency per month	7 ± 8	0–30
Sleep/rest efficiency in actigraphy, %	62 ± 19	16–81
Rest/sleep for 24 h, %	37 ± 12	10–72
Sleep latency, min	8 ± 10	0–38
Sleep efficiency, %	88 ± 9	71–98
REM latency, min	35 ± 62	0–232
Apnea/hypopnea index/h	11 ± 18	0–68
PLMS index/h	15 ± 24	0–70
NREM-1, %	18 ± 6	9–31
NREM-2, %	36 ± 10	19–54
Slow wave sleep, %	12 ± 7	0–22
REM, %	21 ± 8	12–38
Arousal index/h	16 ± 7	7–32
Mean sleep latency in MSLT	1.8 ± 1.2	0.4–4.6
Number of SOREM in MSLT	3.6 ± 0.7	2–4
Mean sleep latency in MWT	6.3 ± 4.1	0.5–15.8
Number of SOREM in MWT	1.1 ± 1.2	0–3
Error % in SCVT	8.5 ± 9.7	0.6–37.8

ESS = Epworth sleepiness score; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test; SOREM = sleep-onset REM period; SCVT = steer-clear vigilance test.

Table 2. Effect of SO on different subjective and objective parameters

Variable	Cases, n	Before SO treatment mean ± SD	After SO treatment mean ± SD	p value
ESS	13	17.8 ± 1	13.9 ± 1.2	0.001
Number of cataplexies/month, median	13	20	1	0.001
Number of sleep paralyses/month	13	4.1 ± 8.3	0	0.011
Number of hallucinations/month	13	7.6 ± 9.5	0.4 ± 1.1	0.005
Nightmares/month	13	6.5 ± 10.3	1.5 ± 5.5	NS
Sleep/rest efficiency in actigraphy	8	60.5 ± 19.7	76 ± 4	0.017
Mean sleep latency in MSLT, min	8	2 ± 1.5	2.4 ± 2.6	NS
Number of SOREM in MSLT	8	3.6 ± 0.5	2.4 ± 1.4	0.038
Mean sleep latency in MWT, min	9	5.5 ± 4.5	17.4 ± 8.9	<0.001
Number of SOREM in MWT	9	1 ± 1.1	0.4 ± 1.1	NS
Error % in SCVT	8	10.8 ± 12.5	2.1 ± 2.1	0.017
Total sleep time in PSG, min	5	390 ± 50	398 ± 42	NS
Sleep latency in PSG, min	5	11.7 ± 16	5.6 ± 7.5	NS
Sleep efficiency in PSG, %	5	88.5 ± 7.9	92.1 ± 5.7	NS
REM latency, min	5	76.6 ± 109.4	21.6 ± 41.9	NS
NREM-1, %	5	19.1 ± 5.5	8.2 ± 2.8	0.071
NREM-2, %	5	38.3 ± 10.2	37.5 ± 9.3	NS
Slow wave sleep, %	5	10.5 ± 7.7	33.1 ± 14.7	0.074
Apnea/hypopnea index/h	5	22.4 ± 27.8	16.2 ± 16.7	NS
PLMS index/h	5	7.1 ± 7.2	8.3 ± 14.8	NS
Arousal index	5	20.5 ± 6.3	9.2 ± 2.3	0.067

ESS = Epworth sleepiness score; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test; SOREM = sleep-onset REM period; SCVT = steer-clear vigilance test.

and persisted in 1 of 4 patients. All patients experienced a subjective improvement of their nighttime sleep. The improvement of the clinical symptoms of NC is presented in figure 1.

Rest/sleep efficiency in the actigraphy improved (from 61 to 76%, $p = 0.017$), the mean sleep latency in MSLT did not differ significantly, the mean sleep latency in MWT increased clearly (from 5.5 to 17.4 min, $p < 0.001$) and the error quotient in SCVT decreased (from 10.7 to 2.1%, $p = 0.017$). In PSG a decrease in sleep latency, REM sleep latency, apnea/hypopnea index, NREM-1, REM and arousal index and an increase in slow wave sleep was observed, although as PSG was available before and after treatment in only 5 patients, the results did not reach statistical significance. The results of the different tests are presented in table 2. An actigraphy and a PSG hypnogram example before and after treatment are shown in figure 2.

Dropouts

In 5 patients the drug was discontinued shortly after initiation due to insufficient compliance (n = 2), lack of efficiency (n = 2) or side effects (n = 1), including nausea and worsening of sleepiness and cataplexy. This patient did not tolerate modafinil and fluoxetine either and did not wish further treatment. Four of these patients had rare cataplexy (once or twice a month); 3 were treated with modafinil (as monotherapy 400–600 mg/day, or together (200 mg/day) with venlafaxine 75 mg/day or fluoxetine 20 mg/day). One patient was treated with clomipramine 100 mg/day. In these patients no follow-up assessment under SO was possible as they discontinued the medication shortly after initiation (1 week in most cases).

Adverse Events

The most common adverse event (considering all 18 patients) was nighttime confusion (n = 6). Others included nausea (n = 2), enuresis (n = 2, in 1 of the cases only once over 1.5 years), diffuse muscle pain, headache, flatulence, disturbance in attention and forgetfulness (n = 1). The patient with diffuse muscle pain also had enuresis; after a dose reduction from 6 to 4.5 g/day the adverse events decreased and the patient insisted on taking the medication. Only 1 patient discontinued treatment because of adverse events. This patient reported pro-

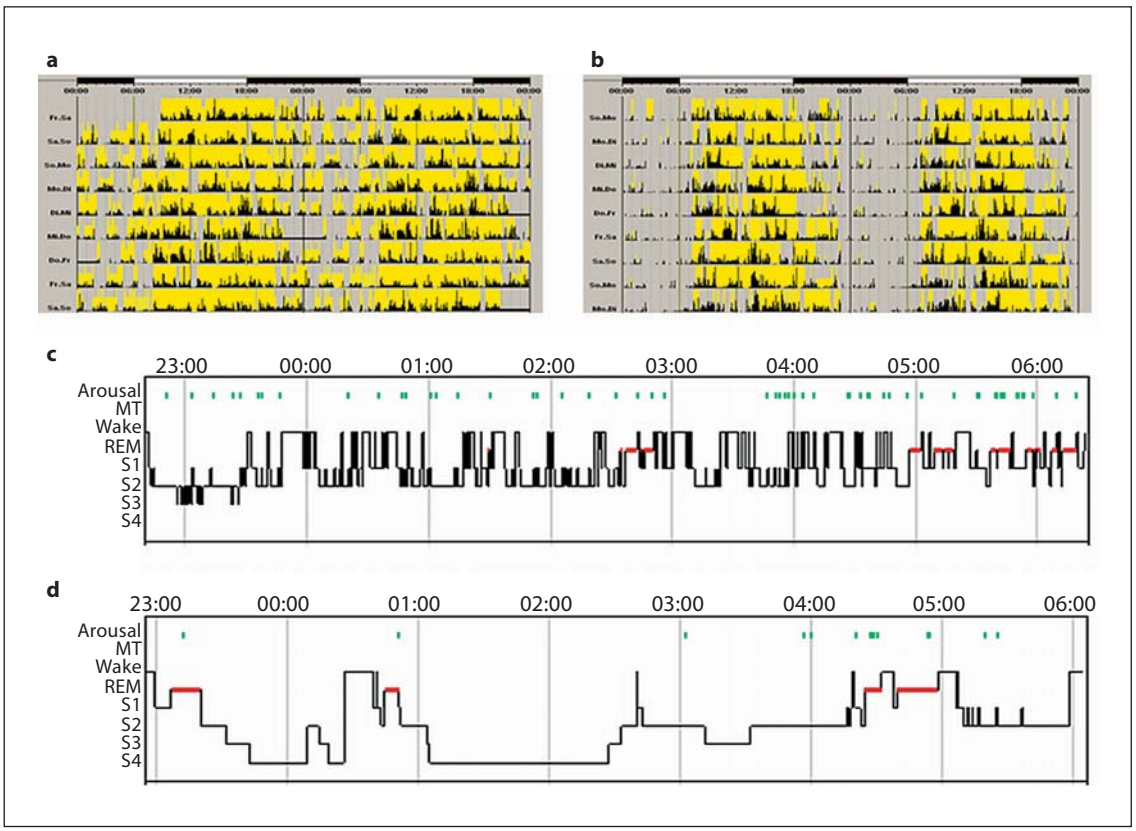

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Fig. 2. Actigraphy and PSG hypnogram examples before and after treatment with SO: **a** actigraphy before, **b** actigraphy after, **c** hypnogram before, and **d** hypnogram after treatment.

nounced nausea and worsening of nighttime sleep and cataplexy.

There was 1 patient who over time voluntarily increased the dose of SO from 2 × 4.5 g to 3 × 4.5 g per night because of nighttime sleep disturbance.

Discussion

Efficacy: Clinical Findings

SO led to significant improvement of cataplexy, daytime sleepiness and alertness, sleep paralysis, hallucinations, nightmares and nighttime sleep. Actigraphy and SCVT were used for the first time to assess the treatment effects of SO.

Cataplexy improvement regarding its frequency, duration and severity has been shown in a number of studies [10–12, 21–27, 34]. As already reported by Mamelak et al. [34], cataplexy under SO occurred later in the day, when the patients were tired. Consistent with previous studies [11, 21, 24, 26, 27, 34], improvement of daytime sleepiness and alertness was demonstrated. As 5 patients were treated with modafinil (in 1 in alternation with methylphenidate) and 1 with fluoxetine, the effects on EDS cannot only be attributed to SO. Sleep paralysis and hallucinations improved too, as previously reported [11–13, 34]. In more recent studies [21, 23–25], a decrease in the frequency of sleep paralyses and hallucinations was observed, but the results did not reach statistical significance. Nightmares disappeared in 3 of our patients, 1 of them reported that she continued dreaming but the dreams were no longer frightening. This phenomenon has also been described by Mamelak et al. [34]. A literature overview of different studies, assessing the effects of SO, is presented in table 3.

Efficacy: Actigraphy, MSLT, MWT, SCVT and PSG

Actigraphy showed a marked improvement in the nighttime rest/sleep efficiency, consistent with the subjectively reported improvement of nighttime sleep. Simi-

Table 3. Literature overview

Reference (first author)	Design	Patients n	Methods	EDS/sleep attacks	Cataplexy	Sleep paralyses	Hallucinations	Nighttime sleep quality
Broughton 1979 [10]	case series, open	16	clinical assessment	improved	improved	NA	NA	improved
Scharf 1985 [11]	case series, open	30	clinical assessment, PSG	improved	improved	improved	improved	improved
Mamelak 1986 [34]	case series, open	48	clinical assessment, PSG, MSLT	improved	improved	improved	improved	improved
Scrima 1989 [12]	double-blind, counter-balanced crossover design	20	clinical assessment, daily diary	not significantly different	improved	NA	NA	improved
Lammers 1993 [13]	randomized, double-blind placebo-controlled crossover design	24	daily diary, questionnaires, PSG, MSLT	improved	improved, but not significantly	low incidence, not accessible	improved	improved, but not significantly
US Xyrem® Multicenter Study Group 2002 [21]	multicenter, double-blind placebo-controlled	136	daily diary, questionnaires	improved, dose-dependent	improved, dose-dependent	improved, but not significantly	improved, but not significantly	improved, dose-dependent
US Xyrem® Multicenter Study Group 2003 [23]	open-label	118	daily diary, questionnaires	long-term improvement	long-term improvement	improved, but not significantly	improved, but not significantly	improved, but not significantly
Mamelak 2004 [24]	open-label study	25	PSG, MWT, questionnaire	improved	improved	improved	improved	improved
Xyrem® International Study Group 2005 [25]	double-blind placebo-controlled	228	daily diary	NA	improved, dose-dependent	improved, but not significantly	improved, but not significantly	NA
Xyrem® International Study Group 2005 [27]	double-blind placebo-controlled	228	daily diary, questionnaires, MWT	improved, dose-dependent	NA	NA	NA	NA
Black 2006 [26]	multicenter, double-blind placebo-controlled	270	daily diary, questionnaires, MWT	improved	NA	NA	NA	NA
Black 2009 [36]	double-blind placebo-controlled	278	daily diary, questionnaires, PSG, MWT	improved	NA	NA	NA	improved

MSLT = Multiple sleep latency test; MWT = maintenance of wakefulness test; NA = not available; PSG = polysomnography.

larly, a significant subjective nighttime sleep improvement [11–13, 34] and a significant decrease in the number of nighttime awakenings have been reported [21, 25]. To our knowledge, actigraphy data has not been previously used to assess the treatment effects of SO. Actigraphy allows the assessment of sleep-wake patterns over longer periods of time. As seen in figure 2, the results are comparable with the hypnogram, obtained after an overnight PSG. We suggest that the method can be a useful, far less expensive and less complex tool in the evaluation of the treatment effects of SO, especially concerning nighttime sleep improvement.

There were no significant differences in daytime sleep latency in MSLT as already reported in the literature [34]. Concordant with previous studies, a significant improvement of the mean sleep latency in MWT was observed [24, 26, 27]. The SCVT demonstrated an improvement in sustained attention. This result can be compared to the

improved ability to stay awake in MWT, but whereas MWT requires a whole day of testing, SCVT is completed in 30 min. Additionally, it is in a way closer to some everyday life situations, where patients are involved in monotonous tasks, but their active participation is still required. We suggest that the test is used complementary to MWT.

SO also leads to changes in nighttime sleep architecture, such as decrease of NREM-1 [24], increase of slow wave sleep [24, 34] and decrease in nighttime awakenings [21, 24]. As PSG was available in only 5 patients before and after treatment, we could not find significant differences in nighttime sleep parameters. Nevertheless, a trend for a decrease in NREM-1 and in the arousal index and a trend for increase in slow wave sleep were observed. Although not significant, there was a decrease in apnea/hypopnea index after SO treatment. This finding is in line with a recent report in which the use of SO 4.5 g/night over 2 weeks did not generate respiratory depressant effects in obstructive sleep apnea patients as measured by the apnea/hypopnea index, obstructive apnea events, central apneas, and oxygen saturation [35].

Safety

SO was well tolerated in most patients. Consistent with the literature [21, 23, 25], adverse events primarily affected the central nervous system and digestive system. In most patients, there was no dose relationship for the most common adverse events and the majority were mild to moderate in severity. In 1 patient, dose reduction led to improvement of the adverse events. Only 1 patient discontinued the medication because of nausea and worsening of the narcolepsy symptoms.

Conclusion

SO is effective not only for cataplexy but also for EDS, sleep paralyses, hallucinations and nighttime sleep quality in NC. The drug is generally well tolerated in spite of the occurrence of mild-to-moderate adverse events. Actigraphy offers a cheaper and less complex alternative to PSG for assessment of SO treatment effects, especially in everyday practice, and vigilance tests should be used complementary to MWT in order to assess sustained attention.

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